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(54) Title: PREVENTION OF NEOVASCULARIZATION OF INTERVERTEBRAL DISCS AND/OR OF TISSUES WITH LOCAL INFLAMMATION

(57) Abstract: The use of an anti-angiogenetic substance for the production of a pharmaceutical preparation for prevention of neovascularization and/or neoinnervation of intervertebral discs and/or of tissues with local inflammation, in particular for prevention of chronic pain, such as chronic low back pain and chronic whiplash associated disorder, is disclosed. Said neovascularization and/or neoinnervation of intervertebral discs may be caused by spinal trauma. Also a method for prevention of neovascularization and/or neoinnervation of intervertebral discs and/or of tissues with local inflammation wherein a therapeutically effective amount of an anti-angiogenetic substance is administered to an individual is disclosed.

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PREVENTION OF NEOVASCULARIZATION OF INTERVERTEBRAL DISCS AND/OR OF TISSUES WITH LOCAL INFLAMMATION

Field of the invention

The present invention relates to prevention of neovascularization and neoinnervation of intervertebral discs and/or of tissues with local inflammation, in particular in order to prevent chronic pain, such as chronic low back pain and chronic whiplash associated disorder.

Background of the invention

Low back pain (LBP):

Low back pain affects approximately 80% of the population during their lifetime in most countries. Except for being extremely common, it is also one of the most costly disorders for the society. In Sweden alone, low back pain was estimated to cost USD 320.000.000 in 1997 (1). The major part of the cost relates to indirect costs such as sick-compensation and reduced productivity, and only a minor part is related to direct costs such as medical care and pharmacological substances.

In a minority of the cases (5%), there may be a known cause for the pain such as intraspinal tumors, rheumatic diseases, infections and more (2). In these cases the treatment may be specifically aimed at the cause. However, in the majority of the cases of low back pain, the cause remains unknown. At present there is no direct way to treat low back pain with an unknown cause and existing treatment modalities only aim at symptomatic relief.

Regarding the societal expenses for low back pain it is well known that 80% of the costs is related to the 10% of the patients that will develop chronic low back pain. The major socioeconomic effects thus relates rather to chronic low back pain patients than to patients with episodes of acute low back pain. It must therefore be considered that it may be even more rewarding, both economically and for the patients, to be able to prevent episodes of acute low back pain developing into chronic conditions, than to treat the acute pain per se.

Whiplash and Whiplash associated disorders (WAD):

About 10% to 20% of the occupants of a stricken vehicle in rear-end car collisions suffer from whiplash injury. The injury may also occur as a result of other types of accidents, such as train accidents, and sudden retardations. This injury is defined as a non-contact acceleration-deceleration injury to the head-neck system. It is most often caused by a rear-end car collision and there is no direct impact on the neck.

Presenting symptoms usually include neckpain, headaches, disequilibrium, blurred vision, paraesthesiae, changes in cognition, fatigue, insomnia and hypersensitivity to light and sound. Dizziness described in a variety of terms such as imbalance, light-headedness and vertigo also occur frequently and these symptoms may be associated with long-term disability.

Although neurologic and orthopedic examinations do not reveal abnormalities in the majority of patients, the characteristics of dizziness due to whiplash can be elucidated by means of ElectroNystagmoGraphic (ENG) evaluation. This examination is a method that is suitable for proving pathology in the oculo-vestibular system of whiplash-patients.

Until recently, the reason for the extent of injury was poorly understood. In addition, due to the legal and insurance issues, the veracity of complaints of neck pain and other symptoms by people who suffer from whiplash is commonly viewed as suspect.

Whiplash injuries can be quite complex and may include a variety of related problems, such as joint dysfunction, and faulty movement patterns, chronic pain and cognitive and higher center dysfunction.

Pathophysiologic aspects of low back pain and whiplash associated disorders.

Acute conditions:

Little is known regarding the exact causes of acute low back pain. This may be due to the fact that LBP is not a specific disease but rather a symptom of various conditions causing pain in the lumbar region of the spine (2). Various medical conditions such as intraspinal tumors, rheumatic diseases, infections as well as injuries to muscles or ligaments in the spine, have all be suggested to induce low back pain (1). The physician may recognize these conditions and a proper diagnosis may be achieved. However, in the majority of the cases (95%) the underlying cause remains unknown. It was recently suggested that a significant part of these cases of acute low back pain may be due to disk-

related substances leaking through the annulus fibrosus, thus irritating the nerve endings located in the superficial layers of the annulus. This leakage may either be seen as annular tears or like silent disk herniations (3, 4). Silent in this regard only implies that the disc herniation did not induce sciatica.

Chronic conditions:

The knowledge regarding the exact cause of the chronic form of low back pain is just as limited as that of acute low back pain (2, 5, 6). However, degeneration of the intervertebral disc has been considered to be one of the most important factors (7, 8). Degeneration of the intervertebral disc may be seen as a "black disc" and may in some cases be treated by surgical stabilization of the involved spinal segment (9). However, the results of such surgery have been debated. It is not known why a tissue like the intervertebral disc may produce pain although there are no nerves in the disc, except for the most superficial layers of the annulus fibrosus (10-12). It is, however, known that nerve endings may be found in the deeper layers, reaching all the way into the nucleus pulposus in injured discs (13, 14). Nerves do not enter new tissues readily, particularly not into cartilage-tissue such as the nucleus pulposus (15). However, it is known that nerves may join newly formed vessels that grow into a scar (16-21). It is therefore assumed that nerves are found in the deeper parts of the disc due to the ingrowth of newly formed blood vessels. These nerves are not just involved in regulating vascular tonus but nerves containing substance P and CGRP have been found in degenerated discs (13, 14, 17, 22-24). Substance P is a neurotransmitter that mainly transmits pain and it is therefore assumed that these nerves induce pain. The pain derived from discs in this fashion is called "discogenic pain" (25).

Tissues with local inflammation:

Similar to the situation of the intervertebral discs, various tissues and structures with an ongoing local inflammatory process are known to be invaded by newly formed vessels and nerves. Such neoinnervation has been suggested to be the main factor for chronic pain and disability in these structures. For instance, it is known that local inflammation in the supraspinatus muscle tendon in the shoulder will lead to neoinnervation of the tendon and that these nerves will produce chronic pain. Attempts have been made to remove these newly formed nerves and blood vessels by surgery.

Summary of the invention

A novel approach to prevent the development of chronic pain syndromes such as chronic low back pain and whiplash associated disorders is to use pharmacological intervention to inhibit the ingrowth of newly formed vessels, and subsequently nerves, into the intervertebral discs after injury. This can be achieved by various approaches; by blocking the activity of substances known to promote angioneogenesis and neovascularization and by using angiogenesis-inhibitors.

It has recently been found that there are various cytokines in the nucleus pulposus (26-30). Some of these substances are known to promote angiogenesis (vessel formation) such as for instance TNF, IL-2, IL-6, IL-8, VEGF, TGF-beta, Basic-FGF and prostaglandins (31, 32). It is known that the annulus fibrosus per se may induce neovascularization (33), but the relationship between the nucleus pulposus-related substances and vascular ingrowth into the disk, in particular into the nucleus pulposus, has never been considered. There are pharmacological substances that may be used for inhibiting these substances. By using such substances it would thus be possible to significantly reduce the risk of newly formed vessels growing into the disk, with subsequent neoinnervation of the disk, and the development of discogenic, chronic pain.

There are also pharmacological substances that act as general angiogenesis inhibitors. They may both inhibit these angiogenetic substances or may also inhibit the formation of new blood vessels in other ways. The use of such angiogenesis-inhibitors would be equally useful for preventing neovascularization and neoinnervation of injured discs.

A third possibility would be to use pharmacological substances that specifically inhibit nerve growth, thereby preventing the neoinnervation of the disc at the site of disc injury.

The timing of the preventive treatment according to the invention is important. The neovascularization is initiated by the disc injury. The injury may present clinically as low back or neck pain. The preventive treatment according to the present invention should thus be started as soon as pain is experienced and continued either until the pain has resolved or preferable until the disc injury has healed. Since healing of the disc may be difficult to determine clinically, one may suspect that treatment for 2-6 months is advisable. In patients were it may be assumed that a disc injury may have been induced, as in the

case of trauma, the treatment should be started as soon as possible after the time of injury.

Detailed description of the present invention

The present invention relates to the use of an anti-angiogenetic substance for the production of a pharmaceutical preparation for prevention of neovascularization and/or neoinnervation of intervertebral discs and/or of and/or of tissues with local inflammation. The invention also relates to the resulting pharmaceutical preparation.

Furthermore, the invention relates to a method for prevention of neovascularization and/or neoinnervation of intervertebral discs and/or of tissues with local inflammation wherein a therapeutically effective amount of an anti-angiogenetic substance is administered to an individual.

The neovascularization and/or neoinnervation of intervertebral discs that can be prevented according to the present invention may be caused by spinal trauma. By preventing this neovascularization and/or neoinnervation of intervertebral discs, it is possible to prevent chronic low back pain and/or chronic whiplash associated disorder.

As stated above, similar to the situation of the intervertebral discs, various tissues and structures with an ongoing local inflammatory process are known to be invaded by newly formed vessels and nerves. Such neoinnervation has been suggested to be the main factor for chronic pain and disability in these structures. For instance, it is known that local inflammation in the supraspinatus muscle tendon in the shoulder will lead to neoinnervation of the tendon and that these nerves will produce chronic pain. In analogy with the pharmacological prevention of neovascularization/neoinnervation of intervertebral discs as discussed, it would thus be possible also to prevent the neovascularization/neoinnervation of tissues with local inflammation with pharmacological inhibition. By preventing neovascularization and/or neoinnervation of tissues with local inflammation it is possible to prevent chronic pain, such as tendinitis. The treatment should be initiated as soon as possible after the injury and continued for 1-6 months.

The anti-angiogenetic substance used according to the invention can either have an indirect anti-angiogenetic effect by inhibiting an angiogenetic substance or a direct anti-angiogenetic effect. The anti-angiogenetic substance

used according to the invention may also have an anti-angiogenetic effect by inhibiting a neurotrophic factor.

The anti-angiogenetic substance used according to the invention may be one of the following substances, or a combination of two or more of the following substances, as well as pharmaceutically acceptable salts thereof.

ANTI-ANGIOGENETIC SUBSTANCES WITH INDIRECT ANTI-ANGIOGENETIC EFFECT BY INHIBITION OF ANGIOGENETIC SUBSTANCES

Angiogenin inhibitors	
Beta-fibroblast growth factor inhibitors	
GM-CSF inhibitors	
Interleukin 2 (IL-2) inhibitors	
Interleukin 6 (IL-6) inhibitors	
Interleukin 8 (IL-8) inhibitors	
Prostaglandin inhibitors	
TGF-beta inhibitors	
TNF inhibitors	
Vascular Endothelial Growth Factor inhibitors	such as P1C11, C225, SU6668, and anti-KDR monoclonal antibodies
Vascular P factor inhibitors	

ANTI-ANGIOGENETIC SUBSTANCES WITH DIRECT ANTI-ANGIOGENETIC EFFECT

TNF inhibitors

Specific TNF inhibitors	
Monoclonal antibodies	such as: infliximab, CDP-571 (Humicade™),

	D2E7, and CDP-870
Polyclonal antibodies	
Soluble cytokine receptors	such as: etanercept, lenercept, pegylated TNF receptor type I, and TBP-1
TNF receptor antagonists	
Antisense oligonucleotides	such as: ISIS-104838
Non-specific TNF inhibitors	
5,6-dimethyl-xanthenone-4-acetic acid (acemannan)	
AGT-1	
ANA 245	
AWD 12281	
BN 58705	
Caspase inhibitors	
CBP-1011	
CC 1069	
CC 1080	
CDC 801	
CDDO	
CH-3697	
CLX 1100	
CM 101	
CT3	
CT 2576	
CPH 82	

CV 1013	
Cyclosporin	
Compounds used in anti-cancer treatment	such as: the binuclear DNA threading transition metal complexes and pharmaceutical compositions comprising them described in WO 99/15535, and methotrexate
Declopramide	
DPC 333	
DWP 205297	
DY 9973	
Edodekin alfa	
Flt ligand (available from Immunex)	
Gallium nitrate	
HP 228	
Hydroxamic acid derivates	
IL-12	
IL-18	
Ilodekacin	
Ilomastat	
ITF-2357	
JTE 607	
Lactoferrin	
Lactoferrin derived or derivable peptides	such as those described in WO 00/01730
Lazaroids; nonglucocorticoid 21-aminosteroids	such as:

	U-74389G (16-desmethyl tirilazad), U-74500	
LPS agonist Esai		
Melancortin agonists	such as HP-228	
Mercaptoethyl-guanidine		
Metoclopramide		
MMP inhibitors (i.e. matrix metalloproteinase inhibitors or TACE inhibitors, i.e. TNF Alpha Converting Enzyme-inhibitors)	such as:	
	Tetracyclines	such as: Doxycycline, Lymecycline, Oxitetracycline, Tetracycline, and Minocycline
	Synthetic tetracycline derivates (CMT = Chemically Modified Tetracyclines)	
	KB-R7785	
	TIMP1 and TIMP2	
	adTIMP2 and adTIMP2	
M-PGA		
Napthopyrans		
NCS-700		
Nimesulide		

NR58-3.14.3	
p38 kinase inhibitors	such as VX-702 VX-745 (Pralnacasan), VX-850, SB-202190, SB-203580, and pyridinyl imidazoles
PCM-4	
PD-168787	
Pentoxifyllin derviates	
Pharma projects no. 6181, 6019 and 4657	
Phosphodiesterase I, II, III, IV, and V-inhibitors	such as: CC-1088, Ro 20-1724, rolipram, amrinone, pimobendan, vesnarinone, and SB 207499
Piclamastat	
PMS-601	
Prostglandins	such as: Iloprost (prostacyclin)
Quinolones (chinolones)	such as: Norfloxacin, Levofloxacin, Enoxacin, Sparfloxacin, Temafloxacin, Moxifloxacin, Gatifloxacin, Gemifloxacin,

	Grepafloxacin, Trovafloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin, Lomefloxacin, and Temafloxacin
RDP-58	
RIP-3	
Sch-23863	
SH-636	
Solimastat	
SR-31747	
Tasonermin	
Thalidomid derivates (or SelCID = Selective Cytokin inhibitors, e.g. thalidomide derivate)	such as: CC-1088 CDC-501, and CDC-801
TNF alpha proteinase inhibitor available from Immunex	
TNF-484A	
Tristetraproline (TTP) (available from Astra-Zeneca)	
VRCTC 310	
Yissum project no. 11649	
Zanamivir	

Eicosanoid synthesis inhibitors

Specific eicosanoid synthesis inhibitors

Monoclonal antibodies

Polyclonal antibodies		
Soluble cytokine receptors		
Receptor antagonists		
Antisense oligonucleotides		
Non-specific eicosanoid synthesis inhibitors		
Betalactames	such as: penicillium, fenoximethylpenicillium, and cephalosporin	
Cyclosporin		
Macrolids	such as: sirolimus, spiramycin, tilmicosin, tylosin, kitasamicin, josamicin, erythromycin, and oleandomycin	
MMP inhibitors (or TACE-inhibitors =TNF Alpha Converting Enzyme-inhibitors)	Tetracyclines	such as: Doxycycline, Trovafloxacin, Lymecycline, Oxitetracycline, Tetracycline, and

		Mino- cycline
	Synthetic tetracycline derivates (CMT = Chemically Modified Tetracyclines) KB-R7785	
Quinolones (chinolones)	such as: Norfloxacin, Levofloxacin, Enoxacin, Sparfloxacin, Temafloxacin, Moxifloxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Trovafloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin, Lomefloxacin, and Temafloxacin	
Thalidomid derivates (SelCID = Selective Cytokin inhibitors, e.g. thalidomide derivate)	such as: CC-1088, CDC-501, and CDC-801	
Inhibitors of enzymes related to eicosanoid synthesis		
Inhibitors of phospholipase A2 (PLA A2)	such as: monoclonal antibod-	

	ies
	polyclonal antibodies
	Lidocaine
	Mepacrine
	Pyrrophenone
Inhibitors of cyclooxygenase (COX) 1 and 2 (i.e. prostaglandin synthesis inhibitors including non-steroidal anti-inflammatory drugs, NSAID)	such as: Acetylsalicylic acid, Monoclonal antibodies, Polyclonal antibodies, Celecoxib, Corticosteroides, Diclofenac, Ibuprofen, Indomethacin, Meloxicam, Naproxen, and Refecoxib

Various inhibitors of angioneogenesis

2-methoxyestradiol,
AG3340 (prinomastat),
Angiostatin,
Anti Integrin alpha-vbeta3,
Batimastat,
Captopril,
Carboxyamido-triazole,
CM101,
Combretastatin,

Contortrostatin,
Curcumin,
Diphenylureas,
Endostatin,
Flavone Acetic Acid,
Genistein,
Human tumor inhibitors,
IL-12,
Irsogladine,
Kringle 5 of plasmino-
gen,
Latent antithrombin,
LM-609,
Marimastat,
Mitoxantrone,
Neovastat Aetherna,
Nigella sativa,
P53 gene therapy,
Pentosan polysulfate,
Peptide delivery system,
PF-4,
PI-88,
Prelatent antithrombin,
PSK,
Recombinant Platelet
Factor 4,
Retinoids,
Scatter factor,
Spironolactone,
Squalamine,
Suramin and suramin
analogues,
Tamoxifen,
Taxol,
Tecogalan,
Tie2 pathway,

Thrombospondin 1 and
2,
TIP-1,
TNP-470 (AGM-1470),
Vinblastine,
Vitamin E, and
Vitaxin®

SUBSTANCES THAT INHIBIT NEUROTROPHIC FACTORS

Substances that inhibit nerve growth factor (NGF)

Monoclonal antibodies,
Polyclonal antibodies
Soluble receptors,
Receptor antagonists,
and
Antisense oligonucleo-
tides

Substances that inhibit brain derived nerve growth factor (BDNF)

Monoclonal antibodies,
Polyclonal antibodies
Soluble receptors,
Receptor antagonists,
and
Antisense oligonucleo-
tides

Substances that inhibit insulin-like growth factor (IGF-1)

Monoclonal antibodies,
Polyclonal antibodies
Soluble receptors,
Receptor antagonists,
and
Antisense oligonucleo-
tides

According to a preferred embodiment, the substance used is a TNF inhibitor. According to an especially preferred embodiment the substance used is

a monoclonal antibody directed against TNF, such as infliximab, CDP-571, D2E7 or CDP-870. According to an other especially preferred embodiment the substance used is a soluble cytokine TNF receptor, such as etanercept. According to an other especially preferred embodiment the substance used is a binuclear DNA threading transition metal complex with anti-cancer effect. According to an other especially preferred embodiment the substance used is a lactoferrin derivable peptide. According to an other especially preferred embodiment the substance used is an MMP inhibitors, such as doxycycline. According to an other especially preferred embodiment the substance used is a p38 kinase inhibitor. According to yet another especially preferred embodiment the substance used is or TTP.

For the purpose of this disclosure the expression anti-angiogenetic substance relates to all substances, compounds, preparations, drugs, and medicaments that inhibit vascular tissue growth and neovascularization.

Furthermore, for the purpose of this disclosure, an inhibitor may be an inhibitor, a blocking agent, a blocking substance, an antagonist, an antibody, a soluble receptor, and/or any other substance that prevents transcription and/or expression.

Also for the purpose of this disclosure, TNF relates to what formerly was called TNF-α.

The term "individual", as it is used herein, relates to any human or non-human mammal in need of preventive treatment according to the invention.

The term "chronic" relates to a condition or pain which has lasted for at least one month.

The substance or pharmaceutical composition according to the invention is administered once or repeatedly until the desired therapeutical effect is obtained. The substance or pharmaceutical composition according to the invention is administered in a therapeutically effective amount, i.e. an amount that will lead to the desired therapeutical effect.

The pharmaceutical composition according to the invention may also comprise other substances, such as an inert vehicle, or pharmaceutical acceptable adjuvants, carriers, preservatives etc., which are well known to persons skilled in the art.

According to one preferred embodiment of the invention, the pharmaceutical composition is formulated as a sustained-release preparation. The sub-

stance according to the invention may then, for example, be encapsulated in a slowly-dissolving biocompatible polymer.

The substances or pharmaceutical compositions according to the invention may be administered in any efficacious way. The substances or pharmaceutical compositions according to the invention may for example be injected via intra-articular, intravenous (i.v.), intramuscular (i.m.), intraperitoneal (i.p.), intrathecal (i.t.), epidural, intracerebroventricular (i.c.v.) or subcutaneous (s.c.) routes by bolus injections or by continuous infusion. They may also be administered orally (per os), e.g. in the form of oral preparations, such as pills, syrups, or lozenges. Furthermore, they may be administered by inhalation. They may also be administered intranasally. Moreover, they may be administered transepidermally, e.g. in the form of topical preparations such as lotions, gels, sprays, ointments or patches. They may also be administered as suppositories. Finally, they may also be administered by genetical engineering.

Examples of suitable doses for different administration routes are given below.

Per os	10-300 mg	
i.m.	25-100 mg	
i.v.	2.5-25 mg	
i.t.	0.1-25 mg	daily - every 3rd month
inhalation	0.2-40 mg	
transepidermally	10-100 mg	
intranasally	0.1-10 mg	
s.c.	5-10 mg	
i.c.v.	0.1-25 mg	daily – every 3rd month
epidurally	1-100 mg	

Examples of suitable doses for different substances according to the invention are given below.

	Preferred dosage	More preferred dosage	Most preferred dosage
Iloprost			
i.v.	0.1-2000	1-1500	100-1000
	(all doses given in µg/kg body weight/day)		
intranasally	50-250	100-150	100-150
	(all doses given in µg/day)		
CC-1088			
Per os	50-1200	200-800	400-600
	(all doses given in mg/day)		
Linomide (Roquinimex®)			
Per os	0.1-25	5-20	10-15
	(all doses given in mg/kg body weight/day)		
HP-228			
i.v.	5-100	10-50	20-40
	(all doses given in µg/kg body weight)		
Ariflo® SB 207499			
Per os	10-100	30-60	30-45
	(all doses given in mg/day)		
KB-R7785			
s.c.	100-500	100-300	150-250
	(all doses given in mg/kg body weight/day)		
Prinomastat (AG3340)			
Per os	1-250	5-100	10-50
	(all doses given in mg for administration twice daily)		
Batimastat			
Per os	1-250	5-100	10-50
	(all doses given in mg for administration twice daily)		

Marimastat			
Per os	1-250	5-100	10-50
	(all doses given in mg for administration twice daily)		
CDC-501			
Per os	50-1200	200-800	400-600
	(all doses given in mg/day)		
CDC-801			
Per os	50-1200	200-800	400-600
	(all doses given in mg/day)		

It is possible to use either one ore two or more substances according to the invention. When two or more substances are used they may be administered either simultaneously or separately.

The substances according to the invention may also be administered in combination with other drugs or compounds, provided that these other drugs or compounds do not eliminate the effects desired according to the present invention.

It is understood that the response by individual patients to the substances according to the invention or combination therapies, may vary, and the most efficacious combination of drugs for each patient will be determined by the physician in charge.

The invention will now be further explained in the following examples. These examples are only intended to illustrate the invention and should in no way be considered to limit the scope of the invention.

Example 1

The intervertebral disc (L4-5) is incised in 60 rats following a left-sided facettectomy. One group of rats receives infliximab 5 mg/kg intraperitoneally (n=10); one group receives a peptide derived from lactoferrin consisting of the amino acid residues in positions 20-31 of human lactoferrin wherein the amino acid residue in position 24 has been replaced with lysine and the amino acid residue in position 26 has been replaced with alanine, i.e. the peptide with the sequence C-F-Q-W-K-R-A-M-R-K-V-R (corresponding to the peptide of Experiment 2 in Example 24 of WO 00/01730) (n=10), one group receives 0.2 ml of 2.5 mg/ml of methotrexate intraperitoneally once a week (n=10), one group

receives indomethacin 2 mg/kg/day (n=10), one group receives 10 mg/kg of a monoclonal antibody towards VEGF after surgery and two weeks after surgery (n=10). The remaining 10 rats do not receive any treatment. After three weeks the rats are killed and the incised discs are harvested. Tissue sections of the discs are immunostained with von Willebrand factor and Ulex europaeus antibodies to reveal the presence of blood vessels, and with substance-P, C-flanking peptide of neuropeptide Y and synaptophysin antibodies to detect nerve endings. Using light microscopy the number of blood vessels and nerves is calculated. The number of blood vessels, as well as nerve fibers, is then found to be significantly lower in all five treatment groups when compared to the non-treated group.

Example 2

The tendon of the semimembranosus muscle on the left side in 60 pigs is injected by carrageenan approximately 30 mm from its insertion to the bone. This results in a local inflammation of the tendon. Ten of the pigs receive the lactoferrin derived peptide described in Example 1, ten pigs receive 5 mg of methotrexate at surgery and one week after surgery, ten pigs receive indomethacin 2 mg/kg/day, ten pigs receive 10 mg/kg of a monoclonal antibody towards VEGF after surgery and two weeks after surgery. The remaining ten pigs do not receive any treatment. After 14 days the tendons are harvested and processed for light microscopy. The tendons are immunostained with von Willebrand factor and Ulex europaeus antibodies to reveal the presence of blood vessels, and with substance-P, C-flanking peptide of neuropeptide Y and synaptophysin antibodies to detect nerve endings. It is then found that the number of blood vessels as well as nerve endings is significantly less in all the tendons from the treated groups as compared to the tendons from the ten untreated pigs.

Example 3

Fifteen pigs (each with a body weight of approximately 25 kg) received an intramuscular injection of 20 mg/kg body weight of Ketalar (ketamine 50 mg/ml; Parke-Davis, Morris Plains, New Jersey), an intravenous injection of 20 mg/kg body weight of Hypnodil (methomidate chloride 50 mg/ml; AB Leo, Helsingborg, Sweden), and 0.1 mg/kg body weight of Stresnil (azaperon 2 mg/ml; Janssen Pharmaceutica, Beerse, Belgium). Anesthesia was maintained

by additional intravenous injections of 2 mg/kg body weight of Hypnodil and 0.05 mg/kg body weight of Stresnil. The pigs also received an intravenous injection of 0.1 mg/kg of Stesolid Novum (diazepam; Dumex, Helsingborg, Sweden) after surgery.

Nucleus pulposus or retroperitoneal fat was harvested from the fifth lumbar disk by a retroperitoneal approach. Approximately 40 mg the nucleus pulposus was placed subcutaneously in 12 pigs and the same amount of retroperitoneal fat was placed in 3 pigs serving as control. Of the 12 pigs which received nucleus pulposus, 3 received treatment with methotrexate in a low dose of 2 ml of 25 mg/ml i.v., 3 received treatment with doxycycline in a does of 100 mg i.v., and 3 received treatment with infliximab in a does 100 mg. The remaining 3 pigs only received an infusion of saline.

After one week the pigs were killed and the transplanted tissues were excised and snap frozen in methylbuturate chilled with liquid nitrogen. Frozen sections were stained for blood vessels using rabbit anti-human von Willebrand factor (Code A0082, Lot 105, Dako, Glostrup, Denmark) and biotinylated goat anti-rabbit Ig (Code E 0432, Lot 029, Dako, Glostrup, Denmark) and visualized using DAB (diaminobenzidin tetrahydrochloride, Sigma-Aldrich, St Louis, MO, USA). The sections were also stained for nerve tissue using monoclonal mouse anti-human neurofilament protein Clone 2F11 (Code M0762, Lot 089, Dako, Glostrup, Denmark) and biotinylated F(ab')2 fragment of rabbit anti-mouse Ig (Code E 0413, Lot 065, Dako, Glostrup, Denmark) and visualized using DAB.

The data are shown in Table 1 and clearly demonstrate that there was no neovascularization and minimal neoinnervation of the transplanted fat tissue. However, in nucleus pulposus in pigs treated with saline both new vessels and new small nerves were clearly present already one week after transplantation. Treatment with methotrexate reduced the quantity and quality of new vessels but not the number of newly formed nerves. However, treatment with doxycycline (metalloproteinase inhibitor) or infliximab (monoclonal antibody to TNF) dramatically reduced the number of both newly formed vessels and nerves.

Table 1

	Quality of vessels [1)]	Quantity of vessels [2)]	Nerve fibers [3)]
Fat (control tissue)	0	0	0
	0	0	(+)
	0	0	0
NP + saline	+	++	+
	++	++	(+)
	++	++	(+)
NP + methotrexate	+	+	+
	(+)	(+)	(+)
	+	(+)	+
NP + doxycycline	++	+	0
	0	0	0
	0	0	(+)
NP + infliximab	(+)	0	(+)
	0	0	0
	0	0	0

[1)] *Quality of vessels:*

0 = no vessels
(+) = small with no lumen
\+ = larger vessels with lumen, also longitudinally cut
++ = vessels like in previous control experiments

[2)] *Quantity of vessels:*

0 = no vessels
(+) = only few vessels
\+ = some vessels
++ = many vessels
+++ = abundant vessels

[3)] *Nerve fibers:*

0 = no nerve fibers
(+) = 1-2 nerve fibers in transplanted tissue
\+ = 3-5 nerve fibers in transplanted tissue
++ = > 5 nerve fibers in transplanted tissue

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CLAIMS

1. Use of an anti-angiogenetic substance for the production of a pharmaceutical preparation for prevention of neovascularization and/or neoinnervation of intervertebral discs.

2. Use of an anti-angiogenetic substance for the production of a pharmaceutical preparation for prevention of neovascularization and/or neoinnervation of tissue with local inflammation.

3. Use according to claim 1, wherein said neovascularization and/or neoinnervation of intervertebral discs is caused by spinal trauma.

4. Use according to claim 1 or 3 for prevention of chronic low back pain.

5. Use according to claim 1 or 2 for prevention of chronic whiplash associated disorder.

6. Use according to claim 2 for prevention of chronic pain.

7. Use according to claim 2 or 6 for treatment of tendinitis.

8. Use according to any one of the claims 1-7, wherein said anti-angiogenetic substance has an indirect anti-angiogenetic effect by inhibition of an angiogenetic substance.

9. Use according to claim 8, wherein said anti-angiogenetic substance is a substance that inhibits a substance selected from the group consisting of vascular endothelial growth factor, vascular P factor, IL-2, Il-6, IL-8, beta-fibroblast growth factor, angiogenin, GM-CSF, TNF, TGF-beta and prostaglandins.

10. Use according to claim 9 for treatment of a low back pain and/or whiplash associated disorder.

11. Use according to any one of the claims 1-7, wherein said anti-angiogenetic substance has a direct anti-angiogenetic effect.

12. Use according to claim 11, wherein said anti-angiogenetic substance is a TNF inhibitor.

13. Use according to claim 12, wherein said TNF inhibitor is a specific TNF inhibitor.

14. Use according to claim 13, wherein said specific TNF inhibitor is selected from the group consisting of antibodies, soluble cytokine receptors, TNF receptor antagonists and antisense oligonucleotides.

15. Use according to claim 14, wherein said specific TNF inhibitor is selected from the group consisting of the monoclonal antibodies infliximab, CDP-571, D2E7 and CDP-870.

16. Use according to claim 14, wherein said specific TNF inhibitor is selected from the group consisting of the soluble cytokine receptors etanercept, lenercept, pegylated TNF receptor type I and TBP-1.

17. Use according to claim 12, wherein said TNF inhibitor is a non-specific TNF inhibitor.

18. Use according to claim 17, wherein said non-specific TNF inhibitor is lactoferrin or a peptide derivable thereof.

19. Use according to claim 17, wherein said non-specific TNF inhibitor is a binuclear DNA threading transition metal complex with anti-cancer effect.

20. Use according to claim 17, wherein said non-specific TNF inhibitor is TTP.

21. Use according to claim 17, wherein said non-specific TNF inhibitor is a p38 kinase inhibitor.

22. Use according to claim 11, wherein said anti-angiogenetic substance is an eicosanoid synthesis inhibitor.

23. Use according to claim 22, wherein said eicosanoid synthesis inhibitor is a specific eicosanoid synthesis inhibitor.

24. Use according to claim 22, wherein said eicosanoid synthesis inhibitor is a non-specific eicosanoid synthesis inhibitor.

25. Use according to claim 24, wherein said non-specific eicosanoid synthesis inhibitor is a non-steroidal anti-inflammatory drug.

26. Use according to claim 22, wherein said eicosanoid synthesis inhibitor is an inhibitor of an eicosanoid synthesis enzyme.

27. Use according to any one of the claims 19-26 for treatment of a low back pain and/or whiplash associated disorder.

28. Use according to any one of the claims 1-7, wherein said anti-angiogenetic substance is a substance that inhibits a neurotrophic factor.

29. Use according to claim 28, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits nerve growth factor.

30. Use according to claim 28, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits brain derived nerve growth factor.

31. Use according to claim 28, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits insulin-like growth factor.

32. Use according to any one of the claims 28-31 for treatment of a low back pain and/or whiplash associated disorder.

33. A method for prevention of neovascularization and/or neoinnervation of intervertebral discs wherein a therapeutically effective amount of an anti-angiogenetic substance is administered to an individual.

34. A method for prevention of neovascularization and/or neoinnervation of tissue with local inflammation wherein a therapeutically effective amount of an anti-angiogenetic substance is administered to an individual.

35. The method according to claim 33, wherein said neovascularization and/or neoinnervation of intervertebral discs is caused by spinal trauma.

36. The method according to claim 33 used for prevention of chronic low back pain.

37. The method according to claim 33 used for prevention of chronic whiplash associated disorder.

38. The method according to claim 34 used for prevention of chronic pain.

39. The method according to claim 34 used for treatment of tendinitis.

40. The method according to any one of the claims 33-39, wherein said anti-angiogenetic substance has an indirect anti-angiogenetic effect by inhibiting an angiogenetic substance.

41. The method according to claim 40, wherein said anti-angiogenetic substance is a substance that inhibits a substance selected from the group consisting of vascular endothelial growth factor, vascular P factor, IL-2, Il-6, IL-8, beta-fibroblast growth factor, angiogenin, GM-CSF, TNF, TGF-beta and prostaglandins.

42. The method according to claim 41, for treatment of low back pain or whiplash associated disorder.

43. The method according to any one of the claims 33-39, wherein said anti-angiogenetic substance has a direct anti-angiogenetic effect.

44. The method according to claim 42, wherein said anti-angiogenetic substance is a TNF inhibitor.

45. The method according to claim 44, wherein said TNF inhibitor is a specific TNF inhibitor.

46. The method according to claim 45, wherein said specific TNF inhibitor is selected from the group consisting of monoclonal antibodies, soluble cytokine receptors, TNF receptor antagonists and antisense oligonucleotides.

47. The method according to claim 46, wherein said specific TNF inhibitor is selected from the group consisting of the monoclonal antibodies infliximab, CDP-571, D2E7 and CDP-870.

48. The method according to claim 46, wherein said specific TNF inhibitor is selected from the group consisting of the soluble cytokine receptors etanercept, lenercept, pegylated TNF receptor type I and TBP-1.

49. The method according to claim 44, wherein said TNF inhibitor is a non-specific TNF inhibitor.

50. The method according to claim 49, wherein said non-specific TNF inhibitor is lactoferrin or a peptide derivable thereof.

51. The method according to claim 49, wherein said non-specific TNF inhibitor is a binuclear DNA threading transition metal complex with anti-cancer effect.

52. The method according to claim 49, wherein said non-specific TNF inhibitor is TTP.

53. The method according to claim 49, wherein said non-specific TNF inhibitor is a p38 kinase inhibitor.

54. The method according to claim 43, wherein said anti-angiogenetic substance is an eicosanoid synthesis inhibitor.

55. The method according to claim 54, wherein said eicosanoid synthesis inhibitor is a specific eicosanoid synthesis inhibitor

56. The method according to claim 54, wherein said eicosanoid synthesis inhibitor is a non-specific eicosanoid synthesis inhibitor.

57. The method according to claim 56, wherein said non-specific eicosanoid synthesis inhibitor is a non-steroidal anti-inflammatory drug.

58. The method according to claim 54, wherein said eicosanoid synthesis inhibitor is an inhibitor of an eicosanoid synthesis enzyme.

59. The method according to any one of the claims 54-58 for treatment of a low back pain or whiplash associated disorder.

60. The method according to any one of the claims 33-39, wherein said anti-angiogenetic substance is a substance that inhibits a neurotrophic factor.

61. The method according to claim 60, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits nerve growth factor.

62. The method according to 60, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits brain derived nerve growth factor.

63. The method according to claim 60, wherein said substance that inhibits a neurotrophic factor is a substance that inhibits insulin-like growth factor.

64. The method according to any one of the claims 60-63 for treatment of a low back pain or whiplash associated disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01115

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/00, A61P 43/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pathology International(2000), Suppl, A17-A31, Volume 50, 2000, A.J. FREEMONT, "Nerve Ingrowth into the Painful Intervertebral Disc: A Target forGene Therapy?", see the whole text --	1,3-5,8-33, 35-37,40-64
X	Journal of pathology (2000) Suppl., Volume 190, 2000, A.J.FREEMONT, "Association between endothelial betaNGF expression in intervertebral discs (IVD) back pain level, neovascularisation, and nerve ingrowth", see the whole text --	1,3-5,8-33, 35-37,40-64

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2002	05-11-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Frida Plym Forshell/LR Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01115

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	New Insight into Disk Pain. Datasheet (online). ORTHO-MCNEIL PHARMACEUTICAL. Retrieved on 2002-09-20 from the Internet: <URL://web.archive.org/web/20000118125320/ http://ultram.com/woc/issue2/insight.htm dated 2000-01-18. See the whole text	1,3-5,8-33, 35-37,40-64
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P,X	A.J. FREEMONT et al.: Mast cells in the pathogenesis of chronic back pain: a hypothesis. Journal of Pathology, J Pathol 2002; 197: 281-285. Published online 21 March 2002 in Wiley InterScience (www.interscience.wiley.com). See page 284, column 1, "conclusion"	1,3-5,8-33, 35-37,40-64
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P,X	JOHNSON, W.E.B. et al.: Immunohistochemical Detection of Schwann Cells in Innervated and Vascularized Human Intervertebral Discs. SPINE Volume 26, Number 23, 2550-2557, 2001. See page 2555, column 2, - page 2556, column 2	1,3-5,8-33, 35-37,40-64
	--	
A	The Lancet, Volume 350, July 1997, A.J. FREEMONT et al., "Nerve ingrowth into diseased intervertebral disc in chronic back pain", page 178 - page 181, abstract	1,3-5,8-33, 35-37,40-64
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X	Joint Bone Spine 2000, Volume 67, 2000, Anne-Joëlle Weber et al., "Angiogenesis: General mechanisms and implications for rheumatoid arthritis", page 366 - page 383, see page 366, column 1, line 1 - column 2, line 11	2,6-7,34, 38-39
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X	Herz 2001;2 (Supplement I), Volume, 2001, Johannes Waltenberger, "Pathophysiologische Grundlagen der instabilen Koronarsyndrome", page 2 - page 8, abstract	2,34
A	abstract	6-7,38-39
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01115

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Current Opinion in Investigational Drugs2001, Volume 2, No 8, 2001, David A Walsh et al., "Angiogenesis: A therapeutic target in arthritis", page 1054 - page 1063, abstract -- --------	2,6-7,34, 38-39

INTERNATIONAL SEARCH REPORT

Int...ional application No.
PCT/SE02/01115

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33-64
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see extra sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01115

Continuation of Box I.1.

Claims 33-64 relate to a therapeutic method practised on the human or animal body, namely methods for prevention of neovascularisation and/or neoinnervation of different body parts by administering an anti-angiogenetic substance. Thus, the International Searching Authority is not required to carry out an international search for these claims (PCT Rule 39.1(iv)). Nevertheless, an International Search has been executed for claims 33-64.

Continuation of Box II.

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

Two different inventions have been identified, namely:

1. Claims 1, 3-5, 8-33, 35-37 and 40-64 relating to a method and use of a substance for preventing neovascularisation and/or neoinnervation in intervertebral discs.
2. Claims 2, 6-7, 34 and 38-39 relating to a method and use of a substance for preventing neovascularisation and/or neoinnervation in tissue with local inflammation.

These inventions lack a common technical feature that defines a contribution over the prior art.